MEDICAL GRAND ROUNDS
Parkland Memorial Hospital
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HOSPITAL ACQUIRED PNEUMONIA

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Case: [redacted]

This 13-year-old [redacted] was admitted on [redacted], 1964, in a febrile, delirious state.

Present Illness: Three days before admission he was struck in the anterior chest with a football helmet. The injury was not particularly severe, although he noted soreness that evening. The subsequent day he returned to school but complained of a headache for which he went to the school clinic. On the day prior to his admission he remained at home, being in and out of bed, with complaints of subjective fever. On the morning of admission his parents found him to be disoriented. When seen by his family physician his temperature was 104° and he was immediately referred to Parkland, arriving at the Emergency Room at 10:45.

Physical Examination: The patient was a thin boy appearing his stated age. Temperature 106°, pulse 140, respirations 36. Abnormalities on physical examination included nuchal rigidity, harshness of the breath sounds. Salient normal findings included absence of heart murmurs, absence of peripheral emboli and no splenomegaly.

Accessory Clinical Findings: On admission the hemoglobin was 13.8 gm.%, leucocyte count 6,200 with 68% segmented and 18% band neutrophiles. Urinalysis was within normal limits and showed a specific gravity of 1.039. Electrolytes revealed hypochloremia. A lumbar puncture was performed which revealed normal pressures, clear spinal fluid which contained a total of 7 cells, 4 neutrophiles and 3 mononuclears. The sugar was 107 mg.%. Chest film revealed extensive bilateral mottled infiltrates suggestive of "blood-borne septic emboli".

Admission Impression and Management: The admitting impression was that of staphylococcal bacteremia. Two blood cultures were obtained and the patient was started on methicillin 2 gm every 6 hours and 5 million units of penicillin G intravenously. This therapy was initiated by 12:30.

Course in Hospital: Blood cultures obtained on admission subsequently revealed coagulase-positive staph sensitive to penicillin at less than 0.3 ug. Sputum culture obtained on admission revealed neisseria species and Streptococcus viridans. Throughout his hospital course he remained febrile. By October 31 there was question of early cavitation on chest x-ray and the patient remained tachypneic. On November 1 it was noted that he was cyanotic on room air and a

tracheostomy was performed. By [redacted] there was evidence of a pneumothorax and right pleural effusion. Thoracentesis revealed the fluid to be sterile. At that time sputum culture revealed Herellea species. By [redacted] the pleural effusion revealed both Herellea and Pseudomonas species. With the development of the empyema, chest tubes were inserted. Because of his progressive pulmonary destruction, vancomycin was added to his antibiotic regimen on [redacted] on [redacted] intravenous chloramphenicol was added when the gram-negative rods were noted. With the identification of the herellea and pseudomonas, colistimethate therapy was instituted on [redacted] On [redacted] the patient developed acute respiratory distress; despite extensive efforts at resuscitation he died.

Post-Mortem Examination: Autopsy examination revealed acute necrotizing bronchopneumonia of a panlobar nature with multiple lung abscesses and bronchopleural fistulae. The histopathology was that of infection due to pseudomonas.

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INCIDENCE

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Table 1 lists the available information concerning the incidence of hospital acquired infections and pneumonia. It is apparent that there is considerable discrepancy between the series. However, as indicated by Drs. Cohen, Fekety, and Cluff (1), the incidence in part is determined by the method of reporting. When a report of hospital

acquired infection is left up to the ward physician the incidence is only 64% of that when such infection is determined by monitoring the culture reports of the hospital bacteriology lab and visiting each patient with a suggestive culture. Kessner and Lepper (2) determined that even monitoring cultures gave a falsely low incidence of hospital acquired infection, since appropriate cultures frequently were not taken. Using cultures as an index, they found that 5% of the persons admitted developed hospital acquired infections, but a careful analysis of uncultured patients revealed that in 10% of the cases descriptive clinical, and/or confirming laboratory data strongly suggested the presence of bacterial infection. Thus, the true incidence of hospital acquired infection was 15% rather than 5%. Only the studies of Kislak and Barrett(and perhaps that of Selwyn, who does not clearly state his methods) assess the incidence of hospital acquired infections by physician visits to every patient admitted during a specified period of time. When the "correction factor" of Kessner and Lepper is applied to all other studies, the incidence of hospital acquired infection is on the same order of magnitude of that of the two more accurate studies. Thus, it appears that approximately 15 out of 100 patients admitted to the hospital acquire infection in the hospital, and that approximately 20 to 35% of these infections are pneumonias. Thus, there are probably 10-15 patients with hospital acquired pneumonia per month on the Medical Service at Parkland Memorial Hospital.

The bacterial etiology of hospital acquired pneumonia from the series where that information is available is listed in Table 2. According to these data, gram-positive cocci and gram-negative rods each account for about one-third of all cases, and the two together account for another 15%. These studies are likely somewhat misleading, however. The studies that implicate staphylococci most commonly are those of Selwyn and Lepper, both of which were carried out in 1960-61. More recent studies indicate that gram-negative bacilli are the more frequent offenders. This is certainly in keeping with the clinical experience at Parkland Memorial Hospital, where staphylococcal pneumonia has been no great problem in recent years.

Selwyn's study was carried out at the University of Edinburgh Hospital where he found that Hemophilus influenza caused 40% of all hospital acquired pneumonias. This is in marked contrast to American workers who rarely find this organism. This dichotomy of observations between British and American studies is also present in the bacterial etiology of acute and chronic bronchitis.

CHANGING SPECTRUM

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Several authors, including those listed here and elsewhere in this bibliography, have observed that antimicrobials do not prevent all deaths from infection, but rather cause a shift from community acquired infections to hospital acquired infections as a cause of death. In the late 1950's and early 1960's it became apparent that gram-negative bacilli were becoming the major threat in this regard. This is, perhaps, best stated by Rogers, whose summary appears below.

"The incidence and nature of infections contributing to death on a single medical service during the periods 1938-1940 and 1957-1958 are analyzed.

"In the pre-antimicrobial period infections caused the death of 57 patients, or 28.5 per cent of 200 patients subjected to autopsy. An additional 51 patients (25.5 per cent) had infections of lesser significance.

"During 1957-1958, 28, or 14 per cent of 200 patients died as a result of microbial infections. Significant but less critical infections were present in an additional 30 patients. Thus, although a reduction in the total number of fatal infections occurred, microbial disease continued to play an impressive part in deaths occurring within a medical unit.

"Striking differences were noted between the two periods

under study in the microbial parasites that produced fatal disease, the place where infection was acquired and the presence of unassociated disease antedating infection.

"In the pre-antimicrobial period the majority of fatal infections were produced by pneumococci, streptococci, tubercal bacilli and staphycocci. These infections commonly arose in otherwise healthy persons in the outside community and were the direct cause of hospitalization. In contrast, fatal infection observed in 1957-1958 were commonly caused by gram-negative bacilli, staphylococci, viruses and fungi. During this period fatal infections commonly arose within the hospital in patients already compromised by other serious diseases.

"Contrary to general belief, fatal staphycoccal infections were not more common in the post antimicrobial period. Antibacterial drugs appeared to select the microbial agents that could produce disease, but did not prevent infection from arising in patients with abnormal resistance to infection already hospitalized with other processes".

CLINICAL PICTURE OF GRAM NEGATIVE BACILLARY PNEUMONIA

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In our experience, with the exception of Klebsiella pneumonia, gram negative bacillary pneumonia is a hospital acquired disease. It occurs in persons of all ages, although it is more frequently found in the elderly. Men and women are effected equally. The patients tend to be suffering from some underlying, serious, usually chronic disease that has necessitated a lengthy hospital stay. The underlying disease has frequently necessitated treatment with some combination of reservoir nebulization, penicillin, "anti-gram positive" agents, broad spectrum antimicrobials, and steroids. The onset of pneumonia is frequently insidious being heralded by fever and pulmonary parenchymal infiltrate. The x-ray appearance is usually that of a bronchopneumonia, most frequently in the lower lobes. Abscess formation may occur, and empyemas are fairly common. The patient is frequently anemic; the white blood cell count may be low, normal or high. Gram negative bacilli are usually seen on sputum examination and are frequently found in pure cultures in the sputum. However, since gram negative bacilli regularly replace the normal oropharyngeal flora in hospitalized patients, demonstration of the bacteria in the sputum in the absence of pulmonary parenchymal infiltrates cannot be taken as evidence of pneumonia. The course of the pneumonia is usually prolonged, and results of specific antimicrobial therapy are not dramatic. The mortality rate is high, although we do not have specific mortality statistics.

The reports of Tillotson and Lerner from the Detroit Receiving Hospital concerning pneumonias caused by gram negative bacilli are somewhat at variance with our experience. These authors, who parlayed a retrospective chart review of 38 patients into 6 separate articles, indicate that the gram negative bacillary pneumonia was the cause of admission to the hospital in 27 of the 38 cases. If one disregards their 10 cases of klebsiella pneumonia, there were 17 of 28 patients with other types of gram negative bacilli that caused a non-hospital

acquired pneumonia. In other respects, their patients are very similar to the experience at this hospital. They found that the mean hospital stay was 27 days, and the overall mortality was 45 per cent. Mortality was highest with pneumonia due to Pseudomonas aeruginosa (72%).

TREATMENT

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As a group, gram negative bacillary pneumonias do not respond promptly to antimicrobials; this is particularly true of pseudomonas. Gentamicin will probably become the antibiotic of choice when it is available commercially. At the present time the combination of colistimethate and kanamycin offers the broadest possible coverage against gram negative bacilli until *in vitro* sensitivities are available for the specific organism being treated.

AUTOPSY FINDINGS IN GRAM NEGATIVE BACILLARY PNEUMONIA

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Sections of the lung from cases of klebsiella pneumonia show marked leukocytic exudation into the alveoli, predominantly polymorphonuclear; serum and fibrin are scant. Pneumonia due to *E. coli* shows patchy atelectasis and emphysema and the cellular infiltrate within alveoli is much less dense. The cells are predominantly mononuclears and red cells with only a few polymorphonuclear neutrophiles within alveoli. Pseudomonal infection of the lung produces a characteristic morphologic lesion. There are well demarcated, firm, necrotic nodules located around blood vessels composed of an amorphous, necrotic coagulum containing great numbers of bacteria. These are accompanied by a minimal inflammatory response in which lymphocytes and monocytes predominate. A striking absence of intact neutrophiles is noted. Vascular thrombosis may be present. This distinctive pathologic

picture is probably due to various of the fractions of pseudomonas that have been described by Liu.

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Hoffman and Finberg (55) were probably the first authors to note an increased occurrence of infection due to Pseudomonas aeruginosa coincident with the use of aerosol equipment. They observed that following the introduction of the use of nebulizers to create a high humidity environment in incubators of infants there was an increased incidence of bacteremia, dermatitis, conjunctivitis, and omphalitis due to pseudomonas. They were unable to isolate organisms from the reservoir jars of nebulizers or incubator walls, and hence implicated the moist environment rather than the nebulization per se as the cause of their findings. Macpherson (56) and Sever (57) next called attention to inhalation therapy as a potential vector of hospital acquired pneumonia when each reported that the water found in humidifying devices was routinely heavily contaminated with a variety of bacteria. Although these authors called attention to a potentially serious problem, the specific results of their investigations was largely without meaning. A humidifying device operates by causing oxygen to bubble through the water in the reservoir causing the oxygen to become saturated with water vapor. In this type of device the water acts as a filter for the gas, and any bacteria present are trapped in the water, so that no bacteria emerge in the stream of gas going to the patient. Indeed, devices constructed on the same principle are utilized to filter bacteria from gas in bacteriological research. Thus, although the humidifier jar may be heavily contaminated, there is no seeding of the patient with the bacteria.

Bishop and his co-workers (58, 59, 61) were probably the first to call attention to the potential danger of mechanical ventilators.

Their methods included only surface swabbing of the ventilators to detect bacterial contamination, and hence they did not clearly establish a causal relationship between the ventilator and the subsequent development of pneumonia. They did not differentiate the importance of bacterial aerosols as compared to surface contamination. Nevertheless, they suggested several reasonable means of sterilizing specific ventilators that are in use in England.

The first definitive study of inhalation therapy equipment as a potential source of nosocomial pulmonary infection was carried out in Dallas in 1964 (62). It was found that most inhalation therapy equipment incorporating reservoir nebulizers that was in use in the major hospitals in Dallas generated aerosols containing large numbers of viable bacteria. The aerosols were of a size capable of penetration beyond the level of ciliated bronchial epithelium. The source of bacterial aerosols was the reservoir nebulizer jet, which was not decontaminated by standard cleaning techniques. The jet served as a nidius to inoculate the reservoir fluid in which the organisms propagated. The specific organisms isolated from aerosols varied from institution to institution. The major contaminants were Pseudomonas species, Flavobacterium species, Herellea species, Alcaligenes species, and Achromobacter species. The particular bacterial species was hospital dependent. Only gram negative organisms were isolated. These contaminants were not benign commensals, and a causal relationship was suggested between gram negative bacillary necrotizing pneumonia and inhalation therapy equipment utilizing reservoir nebulization. Equipment without reservoir nebulizers did not generate aerosols containing numbers of bacteria in excess of numbers of bacteria in ambient air. Brief daily nebulization of 0.25% acetic acid afforded a simple and effective means for the decontamination of inhalation therapy equipment with reservoir nebulizers.

Although equipment utilizing small, medication nebulizers is capable of generating bacterial aerosols, it was not found to do so in routine hospital use. Presumably, the small volume of liquid in the nebulizer was used up so rapidly that there was no reservoir in which bacteria could propagate. If, however, contaminated solutions are placed into the medication nebulizer, they result in a bacterial aerosol which the patient inhales to the alveolar level. A hospital epidemic of klebsiella pneumonia has been reported from Bellevue due to contaminated bronchodilator placed in medication nebulizer (73). During the past 6 months we have had a similar epidemic of Serratia marcescens colonization of the respiratory tract at Parkland. Drs. Luby and Sanders have studied this epidemic extensively, and have shown that it occurred due to faulty technique in handling of medications being placed in the medications nebulizer. Thus, the reservoir nebulizer is not the only potential problem, and continuous

monitoring of techniques in inhalation therapy must be carried out.

For the past 4 years the equipment at Parkland containing reservoir nebulizers has been monitored extensively, and the aerosols from such equipment are now sterile over 90% of the time. Contamination can be prevented by daily cleansing with acetic acid. The following procedure is recommended:

1. Once a day, while the equipment is in use, empty the contents from the reservoir nebulizer jar.

2. Rinse the jar with water.

3. Cover the fluid intake of the tube leading to the nebulizer jet with 0.25% acetic acid (approximately 200 ml in most nebulizers).

4. Replace the nebulizer jar on the nebulizer.

5. Turn on the nebulizer so that the acetic acid is aerosolized throughout the machine. The acetic acid should be nebulized into the room with the equipment disconnected from the patient.

6. Let this nebulize for approximately 10 minutes.

7. Turn off the equipment and remove the nebulizer jar.

8. Discard the acetic acid and rinse the jar with water.

9. Refill the jar with desired medication and place on the machine. The equipment is now ready for use.

10. When the nebulizer fluid must be replenished, always discard the remainder from the jar and use fresh, sterile materials.

Before the equipment is used on another patient, it should be returned to the inhalation therapy department to be disassembled and washed to remove particulate matter. It should then be sterilized in either an ethylene oxide sterilizer or soaked in a phenolic disinfectant, and rinsed with tap water. Acetic acid should then be nebulized through the reassembled apparatus. The equipment may be stored dry in some type of protective covering.

ALTERATIONS IN BACTERIAL FLORA IN HOSPITALIZED PATIENTS

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As I have indicated, the cause of hospital acquired pneumonia has changed in recent years from staphylococci to predominantly gram negative bacilli. It has been assumed by almost all investigators that this is due to the suppression of normal, gram positive flora by antimicrobials allowing the overgrowth of gram negative bacilli. There are several lines of evidence, however, that this is an oversimplified view. First, colonization of hospitalized patients with gram negative bacilli is probably not a new event. The studies of Rithchie (84) and Burn (85) in 1901 and 1934 indicate that autopsied, hospitalized patients in the pre-antimicrobial era frequently had large numbers of gram negative organisms in the lung, although gram negative pneumonia was not the cause of death. Second, it is apparent from several of the studies listed above that hospitalized patients rapidly become colonized with gram negative bacilli even in the absence of antimicrobial therapy. Third, in our autopsy review conducted in 1967 approximately 60% of the patients who died in the hospital had gram negative bacilli in their lungs, whereas only 14% of patients dying outside of the hospital had gram negative bacilli in their lungs. Of the hospitalized patients, only 50% had received antimicrobial therapy before death. Fourth, Dr. Waldemar Johanson has extensive, unpublished observations indicating that normal people, out patients, in-patients on a psychiatry service, and hospital associated physicians and nurses are not colonized with gram negative bacilli in the oral pharynx, but that 30 to 40% of hospitalized, ill patients have such organisms in their pharyngeal flora. In the more seriously ill patients, the numbers colonized with gram negative organisms approaches 60 to 70%, and this is independent of antimicrobial therapy.

Based on these observations, one may postulate that seriously ill patients become colonized with gram negative bacilli for reasons that are at present not apparent. Colonization is independent of antimicrobials. One of the sites of colonization is the oropharynx, and these organisms are aspirated into the lungs (96). If host defense mechanisms are impaired due to serious disease, these bacteria colonize the lungs. This process has probably always occurred to some extent, but modern therapy prevents death from the primary disease and allows the seriously ill patient to live long enough to develop gram negative bacillary pneumonia.

TABLE I

Hospital Acquired Infection

First Author	Hospital	Date	All Infection (% admissions)	Pneumonia (% admissions)
Howe	Mass. Genl. Hosp. (Surgical only)	1950-61	4.9	1.0
Roy	Hosp. for Sick Children in Toronto	1959	6.5	2.8
Selwyn	Univ of Edinburgh Hosp.	1960-61	16.8	1.4
Lepper	Univ. of Illinois Hosp.	1960-62	6.5	1.3
Kislak	Boston City Hosp.	1964	13.5	3.2
McNamara	Univ. of Kentucky Hosp.	1965	6.1	2.3
Thoburn	Johns Hopkins Hosp.	1965-66	4.0	0.8
Barrett	Boston City Hosp.	1967	15.5	5.0

TABLE 2

Bacterial Etiology of Hospital Acquired Pneumonia

Organisms	Selwyn (cases)	Lepper (cases)	Thoburn (cases)	Barrett (cases)	Total (cases)	(Percent)
Staphylococcus aureus	25	109	11	9	154	28.9
Diplococcus pneumoniae	12	0	11	8	31	5.8
Streptococci	1	0	2	0	3	0.5
						35.2
Staph. aureus plus Gram negative bacilli	0	76	3	0	79	14.8
Hemophilus influenza	49	1	2	5	57	10.7
Escherichia coli	24	24	9	3	60	11.2
Klebsiella-Aerobacter	0	31	11	8	50	9.3
Pseudomonas	3	29	8	3	43	8.0
Proteus	5	12	1	2	20	3.7
Multiple Gram neg. bacilli	4	0	0	0	4	0.7
Serratia marcescens	0	0	0	1	1	0.1
						33.0
Unknown etiology	0	0	27	3	30	5.5
Totals	123	282	85	42	532	99.2